What's New in Pediatrics

Treatment of Erythroblastosis

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AFTER two years of trial of substitution transfusion of blood in the treatment of erythroblastosis, this method now can be better evaluated and earlier concepts revised. This presentation, then, will be concerned with the total experiences in Southern California with substitution transfusion, as well as with the mistakes that have been made and with suggestions for the safe and proper use of the procedure.

The substitution or exsanguination transfusion was originally developed in eastern centers in 1946 and 1947 and the first reports were glowing, as they usually are. In Southern California the first such transfusions were done in April 1947, and the poor results were alarming and confusing. There was at hand no set of indications for the procedure; mistakes were made and babies continued to die in spite of this new means of therapy.

For purposes of assay and appraisal, therefore, and to study the community effort rather than that of a specialized hematological center, records of all the cases of erythroblastosis in which substitution transfusion was used in a two-year period ending in April 1949 were gathered together. Comparisons between experience at Children's Hospital, Los Angeles, and that at other Southern California hospitals were made. For comparative purposes, data were gathered also on cases of erythroblastosis in which substitution transfusion had not been used.

Table 1 lists the data, which seem to indicate that substitution transfusion has not lowered the mortality rate in Southern California; in fact, it seems to have raised it. However, most of the cases in which substitution was used were severe, whereas most of those handled conservatively were mild.

In addition, the number of cases of cerebral damage that came to light was most alarming. About 15 per cent of the patients who lived turned out to be abnormal, either athetoid or simply slow in mental development. Similar experience has been reported in the literature. The cause of this brain damage is still unknown. Often the condition occurred in cases which were clinically mild. Most students of the disease feel that the damage takes place in utero and that no procedure will alter the development of this complication. It is interesting that these cases tended to be associated with very high maternal antibody titre. Weiner's original thought that kernicterus was produced by the blocking antibodies and that hemolytic symptoms were produced by agglutinins is no longer tenable because agreement now is general that blocking antibodies are the only cause of all forms of hemolytic disease of the newborn.

TABLE 1.—*Mortality Rates from Erythroblastosis in Southern California*

	Number of Cases	Deaths	%
Cases in which substitution was used	45	13	29
Children's Hospital	16	4	25
Other hospitals	29	9	31
Cases in which substitution was not used: Children's Hospital	35	5	14
Total Children's Hospital experience	51	9	18

Other positive and interesting findings included:

1. The history of a preceding sibling with erythroblastosis did not carry a particularly bad prognosis. This is contrary to the thought of Potter and others.

2. Erythroblastosis occurs most commonly in the second pregnancy.

3. Prenatal antibody titres had a definite correlation with the severity of the disease. However, the author disagrees with many of the workers in the field who state that a very high maternal titre invariably means a serious case with a high death rate. In ten cases in this series the titre was 1:256 or more, yet the patients lived and are well, half of them without having had substitution transfusion.

4. Substitution transfusions definitely cut down the length of hospital stay and the number of subsequent transfusions needed.

One relatively unpublicized procedure which has been most helpful has been the Coombs test, sometimes known as the developing test or the antiglobulin test. With this procedure used on the baby's cord blood it is possible to determine the presence of sensitized cells and the titre of any free maternal antibody, and thus get an idea of the probable severity of the disease—all before the baby may show any clinical evidence of erythroblastosis. Obviously such information is of value in determining whether or not to use substitution transfusion. Sturgeon, in a recent report on the use of the Coombs test, noted that the strength of reaction to the test was in close correlation with the severity of the disease, an observation which has been borne out in the author's

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Presented as Part of a Panel Discussion on What's New in Pediatrics before the Section on Pediatrics at the 78th Annual Meeting of the California Medical Association, May 8-11, 1949, Los Angeles.

TABLE 2.—*Coombs Test Reaction Correlated with Severity of Disease*

	No. Cases	Average Severity (8.0 max.)	Died	Kernicterus
Strong reaction.....	16	Severe (5.6)	5	0
Moderate reaction.....	23	Mod. (3.7)	2	2
Weak reaction	17	Weak (2.5)	0	1

experience (Table 2). Thus it is indicated that substitution transfusion should not be considered if the Coombs test reaction is weak.

In passing, the use of Rh hapten for treatment should be mentioned. This is an extract of Rh positive blood which was developed by Carter. It is lipid in nature and non-antigenic; it is said to specifically inhibit anti-Rh agglutinins and appears to be a hapten. The material was used throughout pregnancy in one very severe case and, in this instance, was of no value. The baby, which was born prematurely at seven and one-half months, was hydropic and died a few minutes after birth. Sturgeon and Strong worked with this hapten serum two years ago and could not duplicate the results reported from the original work. Further work along the line of producing a neutralizing serum to be given the mother during pregnancy is certainly indicated.

Although many errors in technique have been made in use of substitution transfusion, the author feels that this "growing-up" period is now over and in the future the procedure can be used with relative safety and facility. So that others may not fall into error, the following list of dangers is presented.

1. In some cases not enough blood was given. For a baby of any size, at least 500 cc. is needed to supplant approximately 90 per cent of the original blood.

2. Transfusion was too long delayed. It should be done immediately after Coombs test results are known and the type of blood determined.

3. Blood was injected into the umbilical vein. In one case the umbilical vein ruptured, and in another thrombosis developed in the portal vein. The patients died.

4. Calcium was injected into the intravenous tubing. One patient died immediately afterward.

5. Protection of the infant against exposure, before, during and after the substitution, was omitted. Two infants had rectal temperature of 94° on admission to the hospital and two others had very low fluid intake for days before death.

The following plan of procedure eliminates the dangers listed and is relatively simple.

1. A set of indications should be established. (The author considers these factors as criteria: (1) maternal history indicative of erythroblastosis, (2) high maternal antibody titre, (3) baby born with evident disease or developing the disease in eight to 12 hours. Every decision is based upon the Coombs test reaction.)

2. Liaison with the obstetrician should be maintained so that titres are determined and transfusion can be undertaken without delay. In selected cases premature delivery may be indicated. The cord should be left long. It is probably best to clamp the cord early.

3. Helpful laboratory work on cord blood would be a cell count and smear for nucleated red cells, an icteric index, and a Coombs test.

4. The substitution should be as soon as possible.

5. The baby should be kept warm and in an oxygen tent from birth in severe cases.

6. The blood should be drawn out through the umbilicus, using the Diamond plastic catheter, and the substituted blood should be put in through the saphenous vein via a cutdown at the ankle. Two persons should do the substitution and the rate of injection should be exactly equal to the rate of withdrawal so that there is no chance of overloading the circulatory system. A 1:1,000 heparin solution in small amounts may be used to clean out the umbilical catheter if it becomes plugged.

7. Rh-negative, type specific blood should be used—at least 500 cc., and more if the maternal history indicates severe difficulty and the condition of the infant is poor.

8. Calcium is not really necessary. If it is given, it should never be injected into the tubing, but very slowly and directly into the vein.

9. After transfusion, the infant should be given fluids subcutaneously and kept in an oxygen tent.

10. Teamwork should be developed at the hospital among physicians called upon to treat erythroblastosis, so that one may be immediately available to assist the resident and to check on details.

Although substitution transfusion in the treatment of erythroblastosis has given disappointing results in Southern California thus far, technique is improving and ultimately a reduction in mortality rate may be achieved. It is noteworthy that in the last 12 cases (six quite severe) in which the procedure has been used, the patients have all gotten along well. Material for the Coombs test is now generally available to laboratories, and it is recommended that the test be used to assist in planning a course of action.

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